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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,578	05/03/2002	Audrey Goddard	P3230R1C001-168	2392

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 10/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,578	GODDARD ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

Upon further consideration, and in order to make several new references of record in support of the standing utility and enablement rejections, the finality of the previous office action is withdrawn. It is noted that a Notice of Appeal and Appeal Brief have been filed. Applicants can request a refund for the associated fee or leave it as credit for future appeals. The delay and inconvenience to Applicants is regretted.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner Zachary C. Howard.

Specification

The disclosure is objected to because of the following informalities:

1) The disclosure is objected to because it contains numerous embedded hyperlinks and/or other form of browser-executable code. See for example, page 31, paragraph 205 and page 35, paragraph 216. Applicants are required to delete the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

2) An updated priority statement of the instant application's parent provisional and nonprovisional applications should be included in the first sentence of the specification or application data sheet. Specifically, the priority statement should be updated to reflect that application 09/380137 has been abandoned. The priority statement was last updated 9/9/2002.

3) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "ANTIBODY THAT BINDS A PRO1158 POLYPEPTIDE".

Appropriate correction is required.

35 U.S.C. §§ 101 and 112, First Paragraph

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are directed to an isolated antibody that specifically binds to the polypeptide of SEQ ID NO: 68, referred to in the specification as PRO1158. The specification does not disclose any secondary or tertiary structural features of this polypeptide (other than a transmembrane domain; see Figure 68), nor does it assert that the polypeptide has any homology with known, characterized polypeptides. The instant specification does not disclose any additional information regarding PRO1158 such as subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO1158, or what physiological significance PRO1158 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

The record shows that Applicants rely primarily upon the asserted utility disclosed in Example 18, namely that the claimed polypeptides are useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of having a tumor (see, for example, pg 7 of the 3/14/05 response and pg 6-7 of the 8/8/05 Appeal Brief). However, this asserted utility is not substantial for the following reasons.

In Example 18, the specification discloses that PRO1158 tested positive in a differential tissue expression analysis to detect overexpression or underexpression of PRO polypeptides in cancerous tumors (pgs 140-144). Quantitative PCR was used to detect differences in levels of cDNAs in cDNA libraries made from cancerous and normal tissues. Example 18 discloses that PRO1158 cDNA levels are higher in normal lung as compared to lung tumor (see pg 142). There is no disclosure of how great a difference in cDNA levels was detected. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation

between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (2003, Nature Biotechnology 21:976-977).

Furthermore, a substantial utility requires that one of skill in the art be able to use the invention. One of skill in the art would not be able to use the invention because Applicants have provided a single analysis without any relative range for utility based on underexpression of PRO1158 mRNA in lung tumor. Example 18 does not teach how high the expression level is (relative or absolute), what the level of reproducibility or reliability is, whether the results are statistically significant, or the nature or number of samples that were used. It is not clear, for example, if underexpression was detected in 1 out of 10 or 10 out of 10 lung tumors. It is not disclosed what type(s) of lung tumor was analyzed and what stage of differentiation it was at; it is not clear if the finding can be generalized to all lung tumors from that tissue type. It is not clear if the pooled lung tumor sample is made from different types of tumors, and if so, what the ratios are. Valle et al (2003. Expert Rev Mol Diagn. 3(1):55-67) teaches "Lung cancer is a broad term comprising cancers that arise in epithelial tissue in the lining of the bronchi as well as in the trachea, bronchioles and alveoli" (see page 56). It is not clear what type of lung tissue the normal lung tissue comes from, if it is matched with the type of tissue in which the lung tumor originated, and from what patient population it originated. The relevant art teaches that normal tissue in particular patient populations has aneuploid DNA, which could increase the level of expressed mRNA (Hittelman et al, 2001. Ann NY Acad. Sci. 952: 1-12; Fleischhacker et al, 1995. Modern Pathology. 8(4): 360-365). In view of the dearth of information, the skilled artisan would not know if the results were significant or under what conditions a difference in expression could be detected. This information is too sparse to allow the polynucleotide to be used as a diagnostic marker

for lung tumor. The relevant art sets a much higher standard for considering a candidate marker to be useful in diagnosis. Importantly, Valle teaches, in reference to lung cancer markers, "Of all the markers identified, none have achieved sufficient diagnostic significance to reach clinical application" (see Abstract). Valle further teaches, "numerous potential markers have been identified in lung cancer. However, no single marker has so far met sufficient specificity and sensitivity to be recognized of clinically significant value. This is in part due to the heterogeneity of lung cancer pathology and hence of specimens. Also, some alterations are detected not only in cancers but also in high-risk individuals, yet with no evidence of malign disease. The housekeeping nature of the markers identified further limits their specificity" (see pg 60). The instant disclosure lacks the information and guidance to meet the standard in the art to even consider a gene a candidate biomarker for cancer. For example, Wang et al, 2002 (Oncogene, 21:7598-7604) teaches six candidate genes as markers for lung adenocarcinoma. Tumor tissue was used from one particular type of tumor (lung adenocarcinoma) confirmed to contain 50-80% tumor cells and restricted to "well or moderately differentiated adenocarcinoma with wild type ras genotype" (pg 7588-7599) and was compared to normal lung parenchyma. Wang presents a detailed statistical analysis of the level and range of variation of expression in both normal and lung tumor samples that supports the conclusion that each gene expression is a candidate marker (see Table 2 and Figures 1 and 2). The range of variation presented is such that the percentage of normal samples that fall within the range of lung tumor samples is presented, such that a clinician could know what the percentage of normal tissues would appear cancerous when a diagnosis was made.

Furthermore, even if the disclosure were to provide utility and enablement for PRO1158 DNA, it would not provide either utility or enablement for PRO1158 polypeptides or antibodies. The art teaches that in organisms ranging from yeast to human, changes in mRNA levels are not predictive of changes in the encoded polypeptide levels, especially in cancerous cells. For example, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein

spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. also disclose that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is disclosed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Lichtinghagen et al. (2002, European Urology. 42: 398-406) show a similar lack of correlation in matrix metalloproteinases (MMPs 2 and 9 and the tissue inhibitor of metalloproteinases 1 (TIMP-1) in human prostate cancer. After measuring differential expression at both the mRNA and protein level of the genes, they concluded that [C]omparison of mRNA and protein expression of MMP-2, MMp-9, and TIMP-1, respectively, did not show any significant relationships illustrating the necessity to study these components at both molecular levels" (see abstract, pg 398).

The art also shows that transcript levels do not necessarily correlate with protein levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances that varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 proteins in yeast. They concluded that "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by

as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

As supported by the studies cited above, the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels, and the specification of the instant application has not disclosed that the PRO1158 polypeptide is either overexpressed or underexpressed to the extent that it could be use as a diagnostic marker for any cancer.

Given the asserted decrease in PRO1158 mRNA expression and the evidence provided by the current literature, one skilled in the art would not consider it, more likely than not, that a small decrease in expression (no quantitative data provided) would correlate with significantly decreased polypeptide levels. In the absence of information regarding whether or not PRO1158 protein levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1158 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research. Further research needs to be done to determine whether the small decrease in PRO1158 mRNA expression supports a role for the encoded polypeptide as a diagnostic marker in the cancerous tissue, such that the claimed antibodies that specifically bind to the PRO1158 polypeptide could be used in diagnostics. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertion that the PRO1158 polypeptides and antibodies that bind them have utility in the fields of cancer diagnostics and cancer therapeutics is not substantial.

Applicants' arguments as presented in the 8/8/05 Appeal Brief, as they pertain to the above rejections, have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants describe at pages 4-6 the legal standard, burden of proof and standard of proof for utility. The examiner takes no issue with these descriptions.

Applicants describe their asserted utility at pages 6-7 of the 8/8/05 Appeal Brief. The Examiner has addressed *supra* why this utility is not substantial.

Applicants argue at pages 7-12 of the 8/8/05 Appeal Brief that the previous Office Actions did not provide any evidence that one of ordinary skill in the art would reasonably doubt the asserted utility, and have not established a prima facie case that the claims lack utility. Applicants submit that the data in Example 18 are sufficient to establish the asserted utility. Applicants argue that the Examiner has challenged the reliability of the data in Example 18 and the first Grimaldi declaration, but has not supported these arguments. Applicants contend that the USPTO has not offered any arguments or cited any references to establish that the utility is not substantial, and therefore the USPTO has not met its burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement.

Applicants' arguments have been fully considered, but are not persuasive.

The Examiner's position is that the asserted utility is not substantial because the disclosure lacks information and guidance to support a specific and substantial use for the claimed invention. The data submitted in Example 18 are not sufficient to establish the asserted utility for the reasons set forth in the rejection *supra*, and supported by the relevant art cited therein. These reasons are sufficient to overcome the presumption that the asserted utility is not sufficient to satisfy the utility requirement.

Applicants further contend that even if the USPTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one so skilled in the art would be more likely than not to believe that the claimed nucleic acids could be used as a diagnostic tool for lung cancer. Applicants' rebuttal evidence is presented in detail at pg 11-12 of the response. Applicants refer to the previously submitted Grimaldi Declaration (Exhibit 1) as demonstrating that quantitative or precise data is irrelevant, only that a detectable difference is needed. Applicants submit that the results of Example 18 show a detectable difference and therefore demonstrate the utility of PRO1158 in diagnosis of cancer. Applicants submit that Mr. Grimaldi is an expert in the field who conducted or supervised the experiments and the declaration is based on personal knowledge of the relevant facts at issue. Applicants submit that the declaration of Mr. Grimaldi is an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned, and the USPTO must accept such opinions without an adequate explanation of how the declaration fails to rebut the Examiner's opinion. Applicants submit that the USPTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion.

Applicants' arguments have been fully considered, but are not persuasive. To quote MPEP 716.01(c):

> "In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). See also *In re Oelrich*, 579 F.2d 86, 198 USPQ 210 (CCPA 1978)."

In assessing the weight given to the Grimaldi declaration, each of these factors has been fully considered. Furthermore, although an affidavit or declaration that states

only conclusions may have some probative value, such an affidavit or declaration may have little weight when considered in light of all the evidence of record in the application. *In re Brandstadter*, 484 F.2d 1395, 179 USPQ 286 (CCPA 1973) and *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992).

The nature of the fact sought to be established is whether an accurate diagnosis of lung cancer can be made based on any detectable difference rather than quantitative or precise data. While the examiner does not doubt Mr. Grimaldi's declaration that he observed more PCR product in the lung tumor sample than in the normal sample, the examiner does question the significance of the level of difference. Making quantifiable measurement by eye is far less accurate than using laboratory equipment to make the measurements; furthermore a picture of the gel was not submitted for independent evaluation by the Examiner. Furthermore, case law states that the evidence presented must not be directed to information that should have been in the specification to make the disclosure enabling. *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 680 (CCPA 1975). The evidence presented that any detectable visual difference will represent at least a two-fold difference is not information presented in the specification and is therefore not considered.

With regard to opposing evidence, the teachings of Hu et al and LaBaer et al (cited *supra*) were considered; these references caution researchers on drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Furthermore, the teachings of Valle et al, Hittelman et al, Fleischhacker et al, and Wang et al as discussed in the rejection *supra* were considered.

It was fully considered that the expert in the outcome of the instant application is not independent of the inventor or assignee.

It was fully considered that Grimaldi's statement is based on a factual description of the actual gel in question rather than just being an opinion based on a general impression about the field.

In view of the above factors, the Examiner does not consider the Grimaldi declaration sufficient to overcome the rejection. The Examiner does not question Mr.

Grimaldi's declaration that an "increased" amount of PRO1158 PCR product was observed on the gel in the lung tumor sample. But the declaration does not address how a clinician could use the information presented to accurately make a diagnosis of tumor. Even if tissue samples are pooled, about which the first Grimaldi Declaration says, "That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type," [paragraph 5] without knowing the range of variation and source of the pooled samples there is insufficient guidance. If a clinician took a stomach tissue sample from a patient with suspected stomach cancer, what is the likelihood that when compared with normal tissue, the level of PRO1158 mRNA from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? The statement that expression is "increased" in normal tissue does not answer the questions raised above and does not place a specific and substantial use of the nucleic acid or encoded polypeptide in the skilled artisan's hand. The statement that the relative difference in expression is what is important is generally true, but without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of lung tissue that can used, and other questions, the specification has not provided the invention in a form usable by the skilled such that significant further experimentation was unnecessary.

Applicants argue at pages 13-14 of the 8/8/05 Appeal Brief that the lack of a known role for PRO1158 in tumor formation or the development does not prevent its use as a diagnostic tool for cancer.

Applicants' arguments have been fully considered, but are not persuasive. This argument hinges on the interpretation of the term 'role' in the formation or development of cancer. The term 'role' could be interpreted to strictly mean that the PRO1158 protein is a causative agent in the formation of the cancer; however 'role' could also be interpreted broadly to encompass agents that are associated or correlated with the presence of cancer (i.e. that cancer has formed). The Examiner agrees that in order to

use the level of PRO1158 as a diagnostic tool, it is not required that the PRO1158 have a causative role in the formation of the cancer. However, this diagnostic utility does require that expression of PRO1158 in lung tissue is correlated with the presence of lung cancer. As explained in the rejection set forth *supra*, and in response to Applicants' arguments, Applicants have not demonstrated that PRO1158 expression is correlated with the presence of lung cancer.

Applicants argue at pages 14-17 of the 8/8/05 Appeal Brief that the Chen data (cited by Examiner in the Advisory Action and reiterated *supra*) supports Applicants' assertion that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. Specifically, Applicants argue that Figures 2A-2C show a correlation between mRNA/protein pairs for three specific genes, and that this supports Applicants' assertion of a correlation between mRNA and protein changes. Applicants also argue that to determine if there is a correlation between changes in mRNA and changes in protein levels, one would have to conduct experiments where a measurable change in mRNA for a particular gene is observed, and then examine if there was a corresponding change in the level of the corresponding protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While Chen et al. do teach a correspondence between mRNA expression and protein abundance for some genes, this correlation was only observed in 17% (28/165) of the protein spots measured (see pg 311, left column, for example). Chen et al. clearly teach that mRNA levels do not predict protein levels, as they disclose at pg 304 that "[t]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of a protein present in a given cell or tissue" (see pg 304, right column).

Applicants argue at pages 17-18 of the 8/8/05 Appeal Brief that the arguments made by the PTO are not sufficient to satisfy the PTO's initial burden of offering evidence that one of ordinary skill in the art would reasonably doubt the asserted utility. Applicants state that the Examiner's initial burden is to establish that it is more likely than not that a person of ordinary skill would consider that any utility asserted by the applicant would be specific and substantial. Applicants indicate that the Examiner must consider all the relevant evidence of record.

Applicants' arguments have been fully considered but are not found to be persuasive. The Examiner has made a *prima facie* showing that the claimed invention lacks utility and has provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. Essentially, Applicants have not provided evidence to demonstrate that the PRO1158 polypeptide would more likely than not be underexpressed in lung cancer as compared to normal lung tissue. Accordingly, an antibody that binds to the PRO1158 polypeptide of the instant application is not supported by a specific and substantial asserted utility or a well established utility. The Examiner has fully considered all evidence of record and has responded to each substantive element of Applicant's response. It is noted to Applicants that MPEP § 2107.02 (part VI) also states that "where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained".

Applicants argue at pg 20-23 of the 8/8/05 Appeal Brief that if the gene is differentially expressed in cancer versus non-cancer tissue, then the encoded polypeptide and antibodies that bind it are useful in diagnostics. The Declarations of Grimaldi (second declaration) and Polakis discuss the likelihood that if the nucleic acid is differentially expressed in tumors, then the encoded polypeptide will also be. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal

human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. Applicants also assert that the references of Alberts (Exhibits 1 and 2 of Applicants' After Final), Lewin (Exhibit 3 of same), Zhigang (Exhibit 4 of same) and Meric (Exhibit 5 of same) support the statements of Grimaldi and Polakis.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. While the Examiner agrees with the teachings of Alberts and Lewin that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts (Exhibit 1) also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Exhibit 2 at pg 453). Furthermore, while Zhigang provides an example of a high degree of correlation between protein and mRNA expression of a specific antigen the art also teaches, as described *supra*, that in organisms ranging from yeast to human, changes in mRNA levels are not predictive of changes in the encoded polypeptide levels, especially in cancerous cells. Applicants also have submitted Meric et al., 2002, which states the following:

> The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription.

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the

mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974).

Applicants argue at pages 23-30 of the 8/8/05 Appeal Brief that the courts have held that the utility requirement was satisfied in similar cases. Applicants describe two early decisions relating to utility: *Brenner v. Manson* and *In re Kirk*. Applicants then describe three more recent cases that Applicants hold are very similar to the present case: *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q 881 (C.C.P.A. 1980), *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996). Applicants argue the reasoning of the courts in all three cases that "[I]t is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities" applies to the asserted utility for the claimed antibodies of the Instant Application. Applicants further argue that the opinion set forth in *Fujikawa*, 93 F.3d at 1564, *quoting Nelson*, 626 F.2d at 856; *see also Cross*, 753 F.2d at 1051 ("Successful in vitro testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility") also applies to the asserted utility.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. The Examiner does not dispute Applicants' description of the cases. However, the Examiner does dispute that *Nelson*, *Cross* and *Fujikawa* are each very similar to the present case. The fact patterns of the cases cited by Applicants and of the instant application are significantly different, and the court decisions are not binding with regard to the instant rejection. For example, in all three cases the issue was whether or not there was a reasonable correlation between the disclosed *in vitro* results and *in vivo* activity. In each of these cases, the court made a decision in favor of utility where there was a reasonable correlation between *in vitro* tests and *in vivo* activity. However, in the instant application, the specification as

originally filed has not provided *any* evidence demonstrating the polypeptide to which the claimed antibody binds has any biological activity or is more abundant in normal lung tissue samples as compared to lung tumor samples, respectively, either *in vitro* or *in vivo*. Therefore, the issue of whether or not there exists a reasonable correlation between *in vitro* results/activity and *in vivo* results/activity in the Instant Application is irrelevant.

The Examiner believes that all pertinent arguments from Applicants' Appeal Brief, filed 8/8/05 have been considered and addressed above.

35 U.S.C. § 112, 1st Paragraph, enablement

Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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